Pre-Application Meeting

Leadership for HIV/AIDS Clinical Trials Networks

RFA-AI-05-001

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Deputy Director, Division of AIDS, NIAID

Bethesda, Maryland

December 13, 2004

NIAID & Partner IC's

Managing Partners Committee

External Scientific Review Groups

Clinical Research Mgmt Support Contract

Leadership for HIV/AIDS Clinical Trials Networks

Units for HIV/AIDS Clinical Trials Networks

Community Partners

Evaluation Plan

Leadership for HIV/AIDS Clinical Trials Networks

- Translational Research / Drug Development
- Mother to Child Transmission
- Microbicides
- HIV Vaccines
- Prevention of HIV Infection
- Optimization of Clinical Management including Co-Morbidities

Populations

National Institutes of Health
Center for Scientific Review

Form Approved Through 05/2

Department of Health and Human Services
Public Health Services

Grant Application

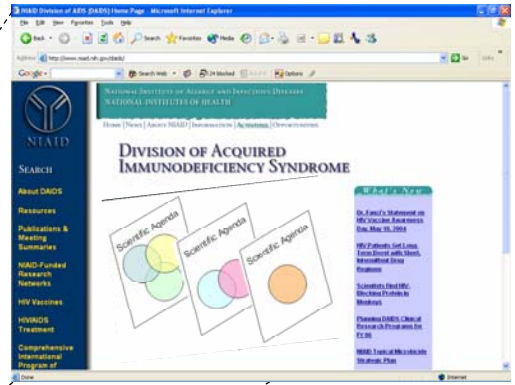
Do not exceed character length restrictions indicated.

1. TITLE OF PROJECT *(Do not exceed 56 characters, including spaces and p*

2. RESPONSE TO SPECIFIC REQUEST FOR APPLICATIONS OR PROGRA
(If "Yes," state number and title)

Number: Title:

3. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR



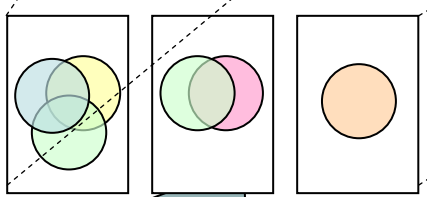
Network Leadership

Coordinating and Operations Center (CORE)

Statistical and Data Management Center (SDMC)

Network Laboratory Structure (NLS)

Potential Clinical Trials Units (CTU) and Research Sites

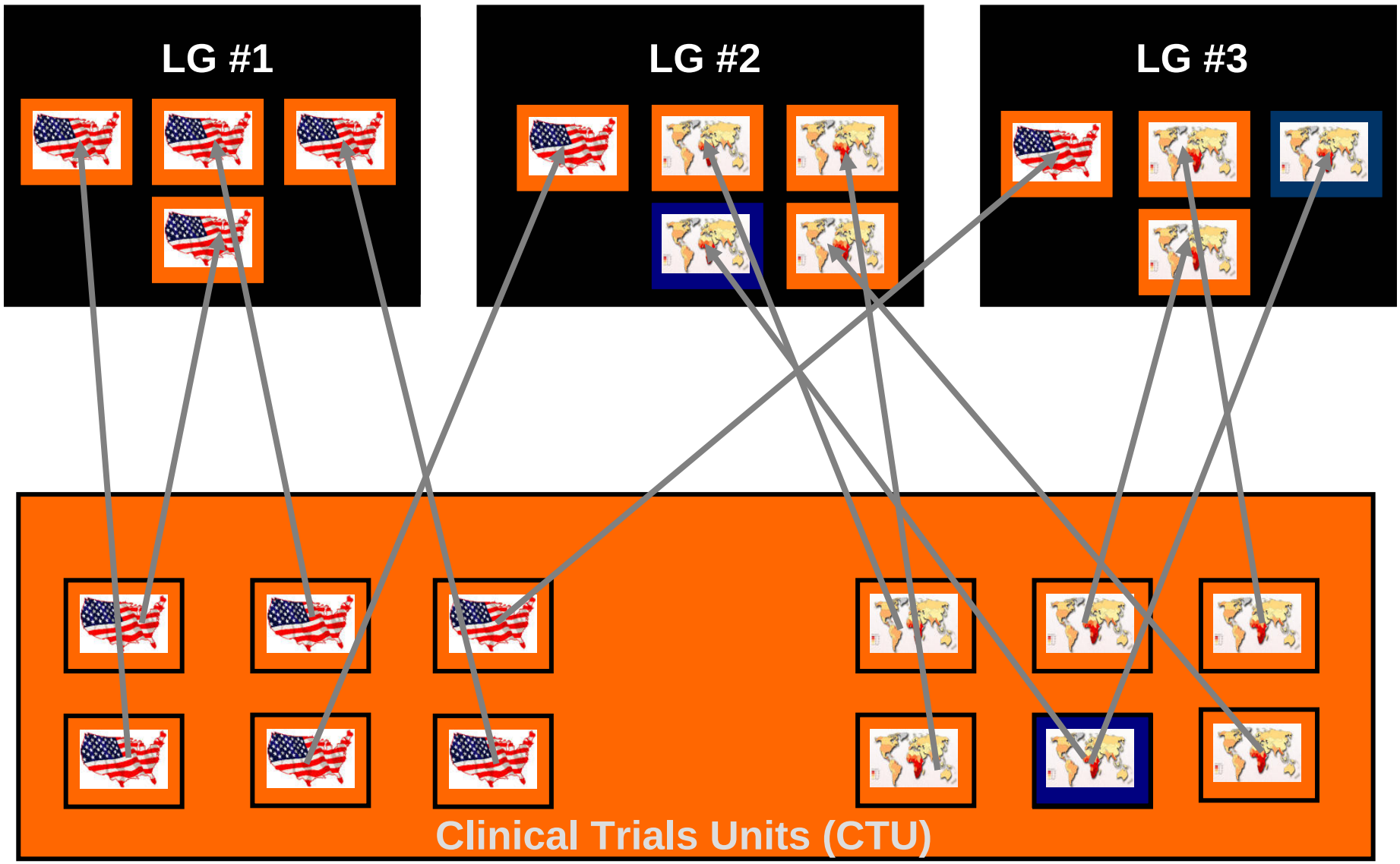


Leadership for HIV/AIDS Clinical Trials Networks

Agenda

Applicant Group

HIV/AIDS Clinical Trials Networks



NIAID & Partner IC's

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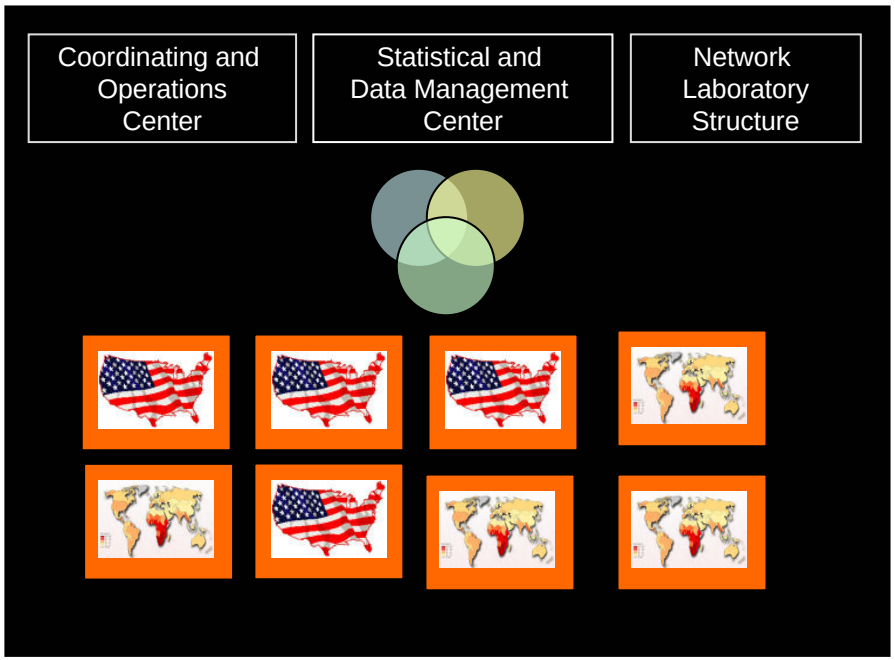
HIV/AIDS Clinical Trials Network



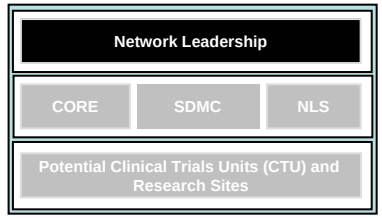
Community Partners

Evaluation Plan

Network Leadership

- Overall responsibility for all aspects of Network functioning
- Propose a research plan for the high priority research area(s) for investigation by the network
- Describe how the networks components will carry out their respective responsibilities and operate in a well-coordinated fashion, to enact the agenda
- Describe any special features in the environment and resources that strengthen the network or make it unique

Network Leadership

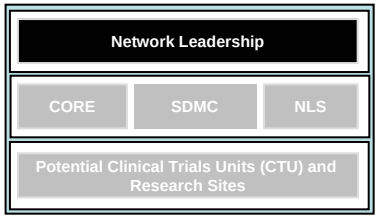


- Executive Committee
  - Governing body responsible for policy, procedures and resource allocation
  - Chaired by CORE PI and includes
    - PI of SDMC
    - PI of Network laboratory structure
    - Director, CORE Operations Center
    - Community representative ($\geq$ 1)
    - Select PIs from clinical research sites
    - DAIDS Project Scientist or designee ($\geq$ 1)
    - DAIDS staff member appointed by DAIDS Project Scientist
    - Representation from ICs providing substantial support

Network Leadership

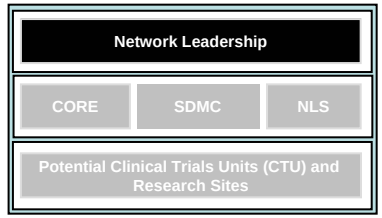
- Scientific Committee(s)
  - Refine Network scientific research plan
  - Oversee protocol development and implementation
  - Provide oversight for ongoing studies
  - Ensure timely publication of results
  - Number and type based on Network agenda
  - DAIDS staff member (≥ 1)

Network Leadership

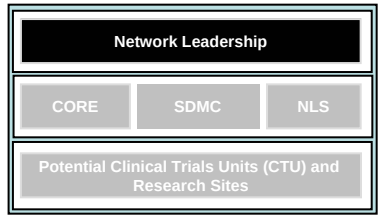


- Resource Committees - Identify and resolve specific functional issues and collaborate across Networks
  - Quality Assurance/Quality Control (QA/QC)
    - Assures data quality at the site level, including protocol adherence, source documentation, and regulatory adherence
  - Site Management and Clinical Care Committee
    - Oversees and resolves operational and clinical care issues identified by affiliated clinical research sites
  - Performance Evaluation Committee
    - Develops and implements standard criteria and processes for assessing progress of each structural component of the Network
  - Data Management Committee
    - Oversees and resolves Network issues pertaining to case report forms (CRFs) and data entry

Network Leadership



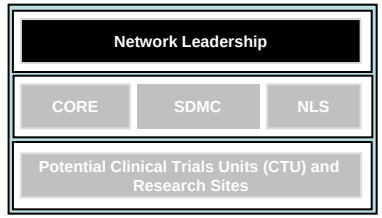
- Resource Committees (*cont.*)
  - Network Community Advisory Board (CAB)
    - Develops and implement a community involvement plan
    - Participates in formulation and implementation of Network research activities
    - Building community capacity goals for conducting specific research activities
  - Training and Education Committee
    - Assesses training needs
    - Implement training activities
    - Evaluate effectiveness of training
  - Pharmacy Committee
    - Collaborate with DAIDS Pharmaceutical Affairs Branch
    - Identify protocol and site specific training needs
    - Provide a forum for communication among Network pharmacists



Additional PI Responsibilities: Monitoring and Compliance

- NIAID policy requires that clinical studies be monitored commensurate with the degree of potential risk to study subjects and the complexity of the study
- All clinical research activities performed through the Network must be in compliance with all U.S. Federal regulations, NIH policies and guidance applying to the conduct of research involving human subjects and FDA requirements for new drug or biological licenses when applicable.
- Each institution engaged in human subjects research has a current, approved Assurance of Compliance Agreement on file with the DHHS Office for Human Research Protections (OHRP)
- Each protocol and informed consent document is approved by the responsible Institutional Review Board (IRB)/Ethics Committee (EC) prior to subject entry
- For Investigational New Drug (IND) studies, each local Investigator of Record supplies a completed and signed FDA Form 1572 to DAIDS for each protocol conducted at each site
- For non-IND studies, each local Investigator of Record provides written documentation of compliance with DAIDS guidelines
- Each study Investigator and sub-Investigator has provided current curriculum vitae to DAIDS
- There is documented evidence of freely given informed consent prior to a participant's entry on study
- All clinical research activities performed outside of the U.S. must, in addition to U.S. Federal regulations, comply with all pertinent host country regulations for human subjects and/or HIV/AIDS research

Network Leadership



Additional PI Responsibilities: Collaboration

Effective coordination of the following common areas:

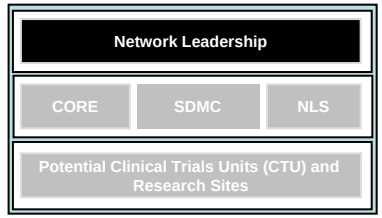
- Development of international clinical research sites
- Harmonization of site operating procedures and quality assurance/quality control of clinical, laboratory, and data management activities
- Development of cross-Network laboratory resources and standard operating procedures (SOPs)
- Procedures for quality and efficiency of specimen management
- Standardization for data management; development of common data elements; development of common data entry interfaces
- Development, training, and support of Community Advisory Boards
- Standardization and shared training for common needs
- Development of cross-Network communication strategies
- Procedures for acquisition and provision of clinical study product(s)

Additional PI Responsibilities: Managing Partners

Managing Partners shall promote joint research activities across Network components

- Maximize use of clinical trial infrastructure and resources across multiple NIH Networks to prevent duplication and to achieve efficiency and economy
- Ensure exchange of current information on the status of protocol development, study conduct and future plans
- Cooperate with DAIDS to develop and implement performance measures for evaluating Network efficiency and effectiveness
- Make recommendations to DAIDS concerning the addition, removal, or consolidation of Network sites or infrastructure assets

Network Leadership



Additional PI Responsibilities: Community Partners

Support Community Partners initiatives and implementing the Community Partners' recommendations. Responsibilities of the Community Partners will include:

- Enhance intra- and inter-network community input
- Identify and develop programs to meet training and support requirements of local and Network CABs
- Increase community representation from resource-limited settings
- Identify and address challenges to participation in clinical trials

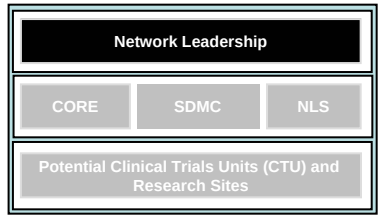
Additional PI Responsibilities: Bylaws, Policies and Procedures

- A Conflict of Interest (COI) Policy consistent with NIH and FDA
- Procedures to ensure adequate protection of the rights and safety of research subjects
- Procedures for maintaining and managing a Protocol Implementation Fund
- Procedures for selecting the most promising candidates to advance in clinical trials
- Procedures to ensure all aspects of protocol development, implementation, quality assurance and oversight meet applicable standards, regulations, and requirements
- Procedures for assessment of Network performance
- Policies and procedures to acknowledge activities of the Network are performed cooperatively with the Division of AIDS, NIAID
- A procedure for submitting, to NIAID, Network related information intended for public dissemination

Additional PI Responsibilities: Bylaws, Policies and Procedures

- **Reporting Requirements**
  - Regulatory reports (e.g. IND reports) as required by the sponsor
  - Administrative reports (e.g. protocol related documents; milestones and other tracking information; patient accrual and demographics; information about clinical research sites, laboratories, etc.; contact information and training records
  - Annual progress report summarizing all research accomplishments and providing metrics on Network performance as a whole and for each of the Network components and participating CTUs to DAIDS.
  - Where applicable, reports shall be provided electronically in accordance with data interchange standards supported by the DAIDS Enterprise System (DAIDS-ES)

Network Leadership



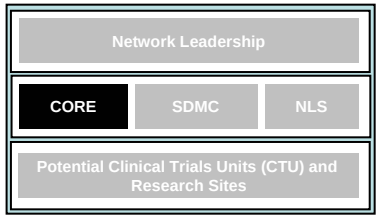
Additional PI Responsibilities: Bylaws, Policies and Procedures

- Publication of Data
  - Prompt and timely presentation and publication of major findings in scientific literature
  - Awardee retains rights to the data, consistent with current DHHS, PHS, and NIH policies;
  - DAIDS, NIAID and other supporting NIH ICs will have access to data

- Investigator Meetings
  - One full Network meeting per year (minimum) in the Washington, DC metropolitan area
  - Network is responsible for logistics, scientific content, and fiscal support of the meetings
  - The meetings must be open to the public, although selected sessions may be closed upon approval of the DAIDS Program Director

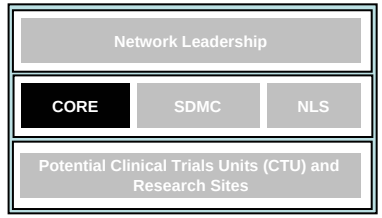
- Demographic Diversity
  - Overall demographic diversity of study participants is reflective of the infected population and those at high risk for infection
  - Established plans for incorporating new sites with access to minority populations and involving new female and U.S. minority investigators

Coordinating and Operations Center (CORE)



- Scientific and administrative leadership, central operations and communications
  - The CORE Principal Investigator (PI) heads the Network Leadership
  - PI responsible for the scientific leadership and administrative coordination of all Network activities, and oversees operations within the CORE
  - PI percentage effort minimum 50%
  - PI may or may not be associated with a CTU
  - A U01 will be awarded to support the Network CORE

Coordinating and Operations Center (CORE)

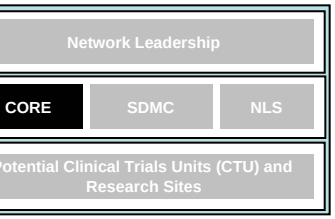


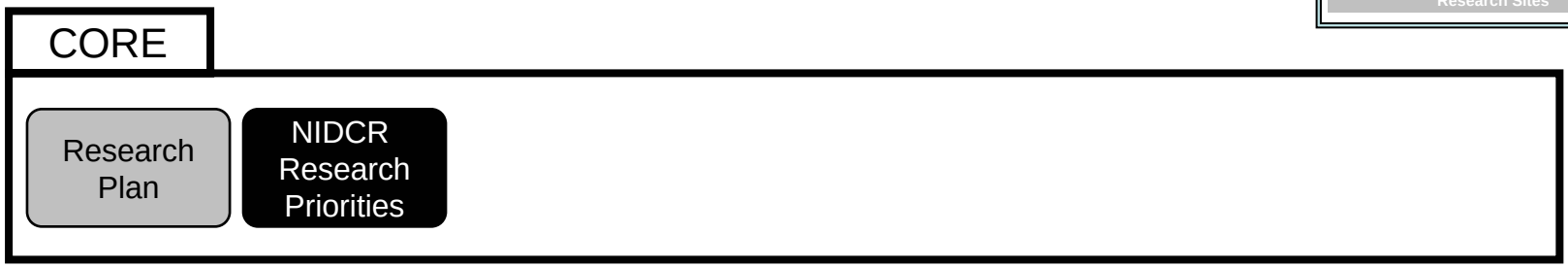
CORE

Research Plan

- Plan for high priority research areas
  - A focused clinical research plan that addresses the most significant issues in the priority research area(s) selected
  - If more than one research area, each to be addressed separately; advantages of a research plan that includes multiple high priority research areas should be discussed
  - May include continuation of clinical trials ongoing in existing DAIDS-sponsored Networks, but must document rationale for continuing such studies and describe how those studies will contribute to the proposed research program

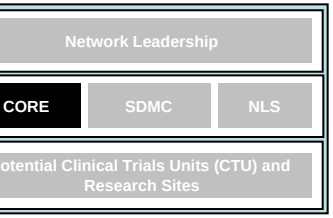
Coordinating and Operations Center (CORE)





- Applicants responding to NIDCR research priorities to include a section entitled “NIDCR research priority area”
  - Proposed clinical research plan
  - Separate budget
  - Organization of scientific committees to develop of an oral health research agenda
  - Operational support
  - Plans for development and evaluation of new concept sheets and clinical trials
  - Network Leadership commitment to oral health agenda

Coordinating and Operations Center (CORE)



CORE

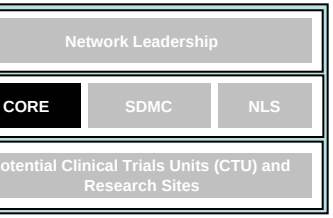
Research Plan

NIDCR Research Priorities

Leadership & Network Structure

- Propose an efficient Network structure containing major elements:
  - Organizational and governing structure
  - Lines of authority, decision making processes, key scientific participants
  - Processes and timelines for establishing bylaws, policies, and procedures
- A plan to incorporate new, minority, and women Investigators into the Network's activities
- Policy and procedures to plan for the expenditure and management of Protocol Implementation Funds

Coordinating and Operations Center (CORE)



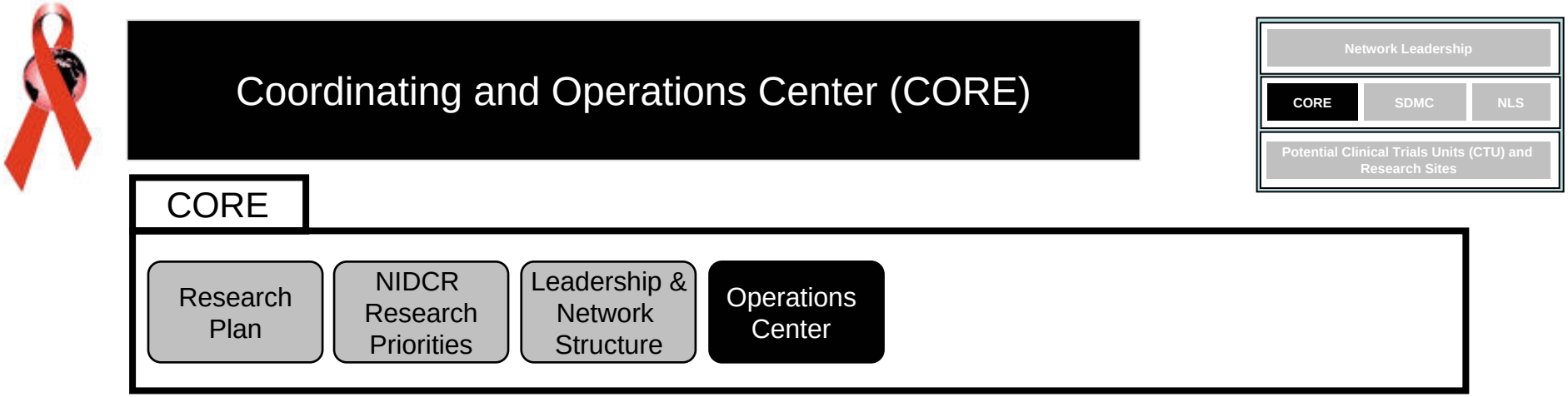
CORE

Research Plan | NIDCR Research Priorities | Leadership & Network Structure

Transition

- Identify clinical research activities and components ongoing at the time of award, their status, anticipated timeline and approximate costs for completion, including site costs
- Identify existing clinical trials infrastructure, clinical trial materials and completed case report forms, requiring phase-out and propose a schedule and budget
- Identify clinical research sites in development and propose milestones, timeline and phase-out budget
- DAIDS to provide annual opportunities for institutions to apply for funding as clinical research sites or Clinical Trial Units
- Transition budgets should not be included in the proposed CORE budget; suggested summary sheets and tables are provided on the RFA website

Coordinating and Operations Center (CORE)



- Coordinate protocol development and implementation
- Establish timelines and specific milestones for protocols
- Report deviations from timelines and initiate corrective actions
- Develop and apply quality guidelines to ensure that all final protocols and related documents are complete and accurate prior to submission and distribution
- Coordinating SOP development
- Coordinate protocol development with product availability
- Track progress of study implementation (e.g. site registration, initiation, regulatory documentation, and accrual)
- Provide administrative support for CORE PI, scientific and resource committees, Network CAB(s), and Network meetings

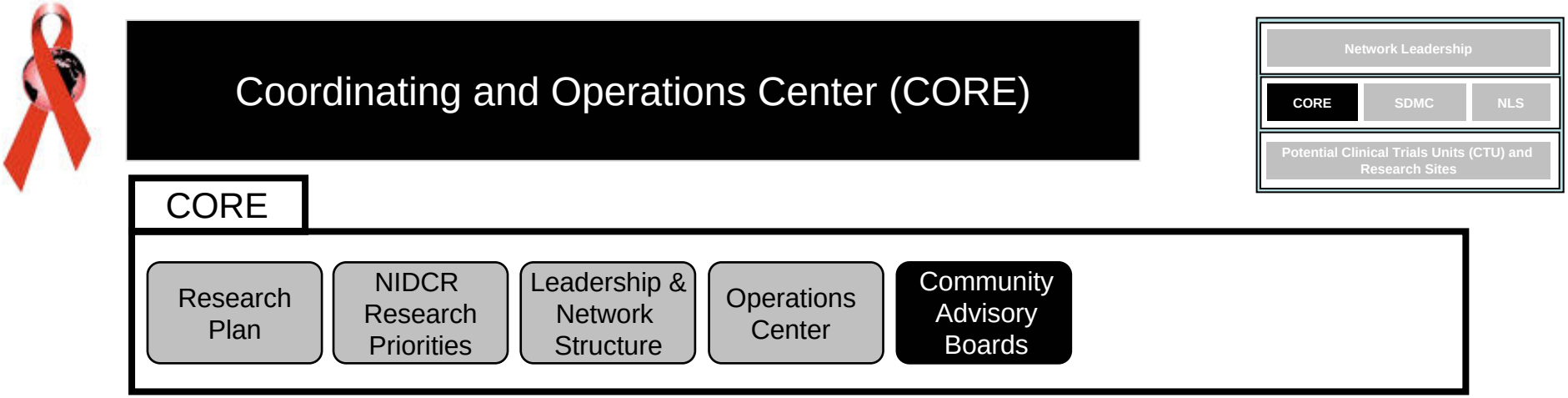
Coordinating and Operations Center (CORE)

CORE

Research Plan | NIDCR Research Priorities | Leadership & Network Structure | **Operations Center**

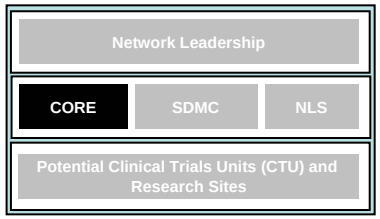
- Provide support to local and national CABs by staff with expertise in community education, training, or activism
- Maintain Network records and archives (e.g. administrative, scientific documents)
- Track site-specific and Network regulatory documents
- Provide routine, ad hoc and urgent reports to DAIDS upon request
- Provide fiscal management and oversight of Network resources, including negotiation and oversight of subcontracts
- Provide scientific, protocol-specific, and other training as required to Network and cross-Network personnel, including DAIDS contractors
- Facilitate cross-Network collaborations by serving as a central coordination resource
- Participate in cross-Network activities as subject matter experts as needed
- Provide administrative support for meeting organization, documentation and logistics upon request from the Managing Partners or DAIDS

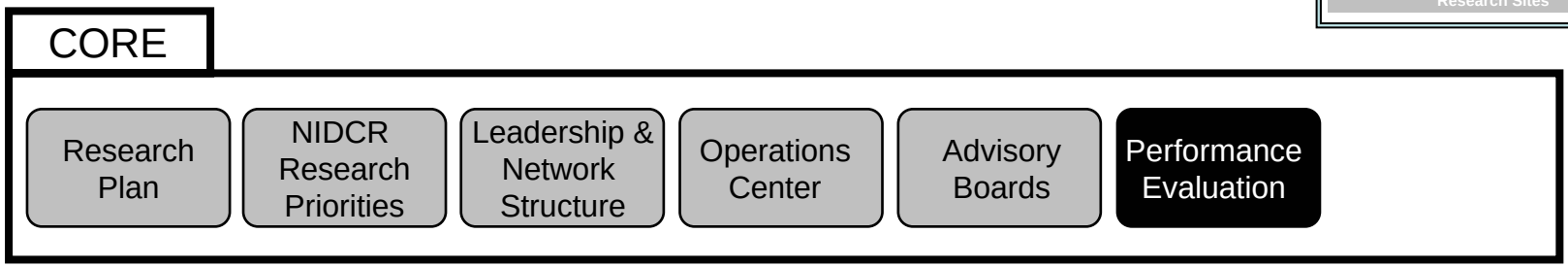
Coordinating and Operations Center (CORE)



- Describe organizational structures and Network policy and procedures for ensuring community input and community representation
- Describe local community representation at CTUs & clinical research sites
- Describe representation on scientific and resource committees, protocol development, implementation and oversight
- Identify means by which Network will facilitate and support activities of CAB(s), including provision of awareness, training, education, and resources required to meet community goals

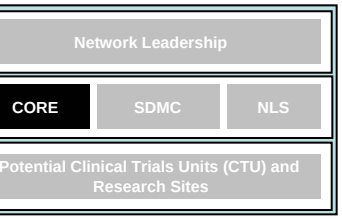
Coordinating and Operations Center (CORE)





- Describe criteria and processes for ongoing evaluation and problem resolution of all Network components, including:
  - CORE
  - CORE Operations Center
  - Statistical and Data Management Centers
  - Network Laboratory Structure
  - Committees & Protocol teams
  - Clinical Trials Units and clinical research sites.

Coordinating and Operations Center (CORE)



CORE

Research Plan	NIDCR Research Priorities	Leadership & Network Structure	Operations Center	Advisory Boards	Performance Evaluation	Cross-Network Collaboration

- Identify network strengths in key areas and propose substantive contributions to a cross-Network, interdisciplinary research agenda
- Describe how the Network proposes to interact with other NIAID/NIH-sponsored HIV/AIDS Networks
- Applicants proposing clinical research in adolescents should make every effort to establish collaborative relationships with other IC HIV/AIDS related programs
  - NICHD-sponsored ATN: RFA HD-04-025 *Adolescent Medicine Trials Network for HIV/AIDS Interventions* is intended to solicit applications for this Network during approximately the same timeframe as this solicitation.
- Applicants proposing clinical research in HIV/AIDS related malignancy should make every effort to establish collaborative relationships with other IC HIV/AIDS related programs
  - NCI will issue an RFA in early 2005 to solicit applications for the *AIDS Malignancy Consortium*

Statistical and Data Management Center (SDMC)

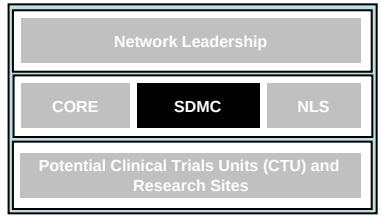
- The Statistical and Data Management Center (SDMC) will provide leadership for:
  - Statistical expertise that complements the Network clinical research plan
  - Innovative approaches to clinical trials methodology
  - Design, conduct, analysis and publication of Network clinical trials/studies
  - Central data management capability that includes randomization, dataset and case report form design, central storage, security, processing and retrieval of study results
  - Data management training throughout the Network
  - Cross-Network efforts in developing common data elements and data interfaces

Statistical and Data Management Center (SDMC)

SDMC Functions: Statistical Research and Analysis

- Participate in the design, conduct, analysis, and publication of clinical research
- Perform timely interim analyses of safety and efficacy
- Produce interim and close-out study monitoring reports
- Generate executive summaries of near-final study results in conjunction with protocol team members
- Perform final analyses for publication, participate in writing scientific papers, and publishing study results
- Perform cross-protocol or cross-study analyses utilizing data from multiple sources within and external to the Network
- Conduct analyses and prepare summary tables for annual and interim reports for DAIDS-sponsored INDs
- Develop innovative clinical trial designs and analysis methodologies consistent with and in support of the Network research plan
- Conduct secondary analyses of Network data to improve the planning, design, conduct and interpretation of future trials
- Providing other analyses and/or reports as requested by DAIDS

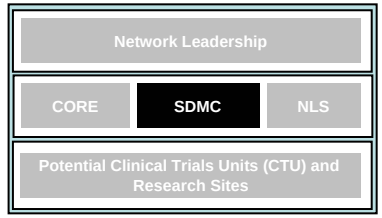
Statistical and Data Management Center (SDMC)



SDMC Functions: Inter-Network Collaboration

- Work cooperatively with counterparts from other DAIDS-sponsored Clinical Trials Networks and other NIH HIV/AIDS-related clinical research programs to develop common data elements and procedures
- Develop approaches for adapting current database systems and structures to accommodate multi-network collaborations, including approaches to maintaining legacy database systems
- Collaborate with other HIV/AIDS clinical research groups, including clinical trial Networks and epidemiologic groups, and DAIDS in creating and exporting datasets for meta and epidemiologic analysis
- Transfer data and exchange data through the DAIDS ES

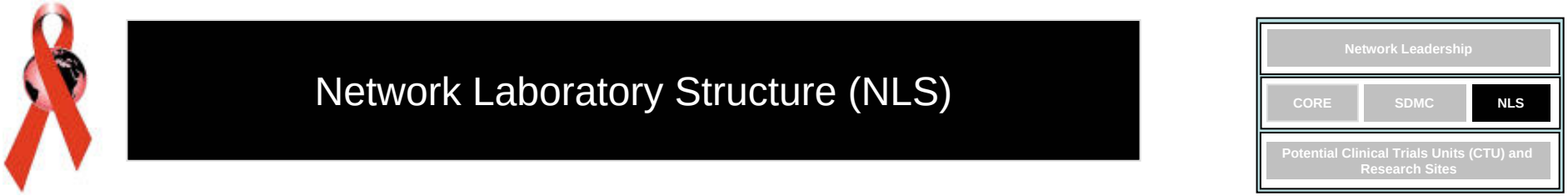
Statistical and Data Management Center (SDMC)



SDMC Functions: Data Management

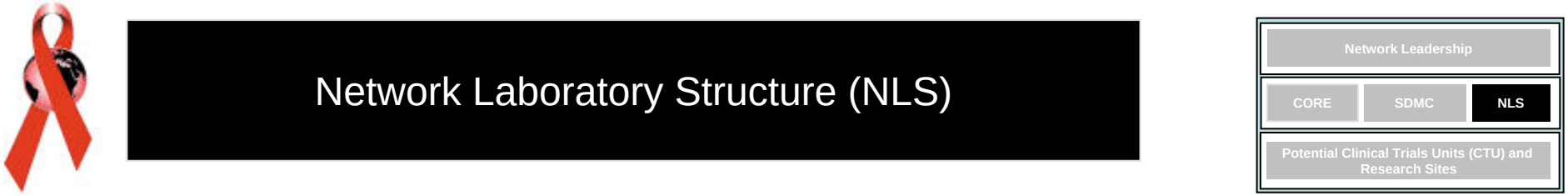
- Provide central registration and support for randomization of all study participants
- Develop case report forms and standardized criteria for clinical endpoint verification
- Provide data management training to the clinical sites and DAIDS' Clinical Site Monitoring Contractor
- Assist in the development of data management resources at sites in resource poor settings
- Provide for central storage, security, processing and retrieval of study results
- Demonstrate means to ensure security and confidentiality of all records containing volunteer identifiers
- Prepare selected public access datasets
- Provide recruitment, retention and other relevant summary data to the sites and protocol teams as designated by the Network Leadership
- Facilitate tracking and identification of laboratory specimens
- Provide clinical research units with limited online access to their own blinded data in the central database
- Develop reports detailing site performance of data management
- Provide annual demographic reports according to NIH policy
- Capture data concerning adverse events and generate periodic reports
- Use MedDRA dictionary for classifying and coding types of EAE

Network Laboratory Structure (NLS)



- Provide laboratory services to support the clinical research agenda:
  - Organizational structure and management plan for the Network Laboratories
  - Role, experience and expertise of NLS staff in the development and execution of required laboratory work
  - Innovative approaches for identification and evaluation of new tests, reagents, and instruments for clinical studies, including collaborations with non-Network laboratories and experts
  - Procedures for conducting and reporting laboratory studies
  - Central laboratories encouraged for end-point assays

Network Laboratory Structure (NLS)



NLS Functions: Laboratory Facilities

Each NLS facility will:

- Secure facilities with adequate space, appropriate layout and necessary equipment, and provide for personnel and study participant safety and the safe handling of infectious and biohazard materials
- Sufficient, properly trained and experienced staff and a suitable staffing structure
- Establish and follow standard operating procedures (SOP) to ensure specimen integrity, effective specimen management and tracking at all stages
- Include a laboratory data management approach and system that allows for efficient, safe, complete, accurate and timely data acquisition, recording, reporting, export and archiving
- Ship specimens in accordance with applicable regulations
- Maintain updated government permits to import and export infectious and non-infectious biological materials
- Make specimens available for cross-trial and cross-Network evaluation
- Establish and follow SOPs to prevent release of specimens for purposes for which the subject has not provided consent

Network Laboratory Structure (NLS)

NLS Functions: Quality Assurance

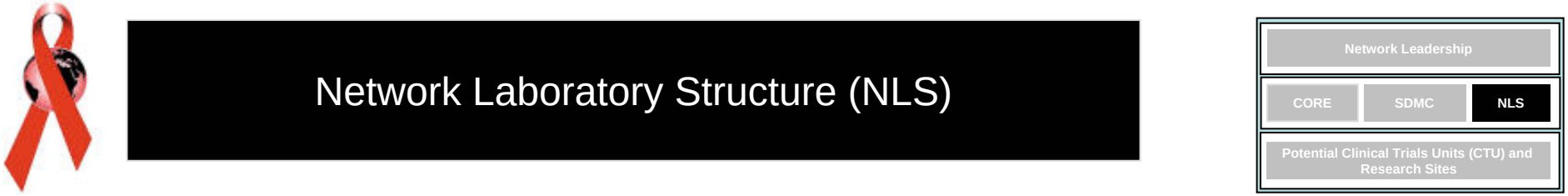
- Provide quality assurance oversight for Network-specific tests and other tests not covered by DAIDS contract resources including:
  - Assessment of laboratory ability, readiness and capacity to support Network research (where applicable, to GLP standards)
  - Provision of training and trouble-shooting
  - Assistance in implementing general and study-specific QA/QC measures
  - Assistance in preparing laboratories for participation in external proficiency testing
- Ensure that QA/QC central provider(s) supply tools to capture information such as test results, methods and instrumentation used, proper use and storage of reagents and timeline for reporting test results
- QA/QC central provider(s) to receive and analyze test results and notify laboratories of proficiency testing results and performance status
- Additional measures to ensure the quality of performed tests, such as confirmatory retesting of samples to be implemented as required
- All laboratories shall cooperate with QA/QC providers

Network Laboratory Structure (NLS)

NLS Functions: Good Laboratory Practices (GLP)

- Where applicable, domestic and international laboratories performing tests that determine safety of interventions or that are used to make subject management decisions, must conduct operations under GLP conditions and must be monitored by external proficiency testing schemes
- Domestic labs that perform these tests must be CLIA-accredited/certified
- International laboratories in resource-developed countries must be certified by their own national accreditation organization, and must strive to achieve equivalent accreditation/certification
- Laboratories performing endpoint testing to determine product efficacy must conduct operations under GLP conditions, are subject to GLP audits, and must receive a satisfactory evaluation when an audit is performed

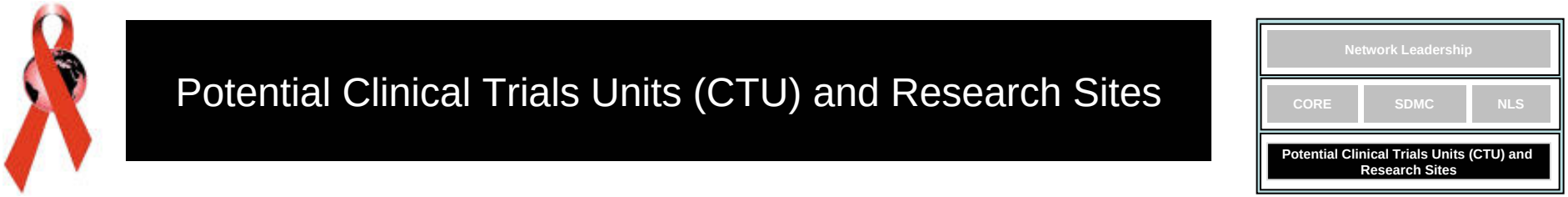
Network Laboratory Structure (NLS)



NLS Functions: Inter-Network Collaboration

- Describe how the NLS will cooperate with counterparts from other DAIDS-sponsored Clinical Trials Networks (and other NIH HIV/AIDS-related clinical research programs as required)
- Describe common platforms and SOPs for testing, laboratory data capture tools, and specimen acquisition, processing, storing, tracking and shipping
- Collaborate with non-Network expert investigators and laboratories when identifying, evaluating and implementing new tests, reagents and instruments for clinical studies
- Transfer technology and share scientific information between NLS located in the US and resource-limited countries

Potential Clinical Trials Units (CTU) and Research Sites



- Approximate number and capacity of clinical research sites required
- Describe the criteria for selection of CTUs and clinical research sites
- For CTUs named in the CORE application, describe site expertise, experience in HIV clinical research and how the site will contribute to the Network research plan
- All proposed sites, regardless of location, should meet basic requirements for the conduct of clinical research and be able to initiate subject recruitment within the first 6 months of award

  – **NOTE 1:** Applications for CTUs will be solicited, submitted, reviewed and funded under a separate but linked RFA: “Units for HIV/AIDS Clinical Trial Networks”; details on proposed CTUs and sites are not required in “Leadership” application

  – **NOTE 2**: DAIDS will require that each Clinical Research Site maintain an average monthly census of 20 participants over a 12 month period for each Network

  – **NOTE 3:** Applicants must not include CTUs or Clinical Research Sites in the CORE organizational structure or costs for CTUs within the CORE Budget

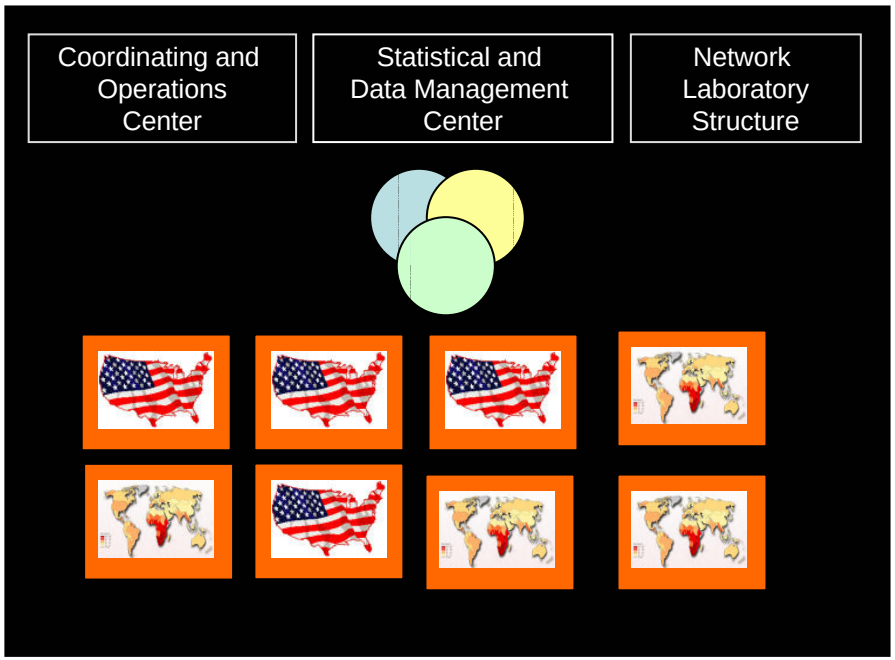
NIAID & Partner IC's

Managing Partners Committee

External Scientific Review Groups

Clinical Research Mgmt Support Contract

HIV/AIDS Clinical Trials Network



Community Partners

Evaluation Plan